

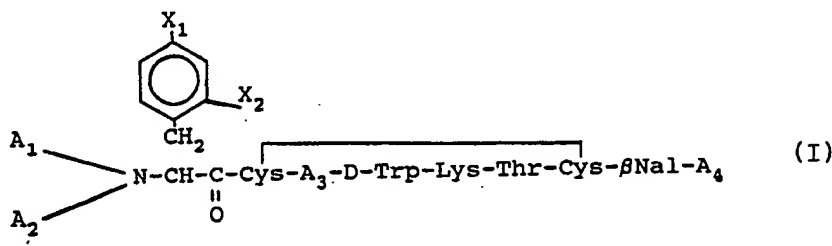


AT

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07K 7/26, A61K 37/02	A1	(11) International Publication Number: WO 91/09056 (43) International Publication Date: 27 June 1991 (27.06.91)
(21) International Application Number: PCT/US90/07074 (22) International Filing Date: 4 December 1990 (04.12.90) (30) Priority data: 447,876 8 December 1989 (08.12.89) US (71) Applicant: THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND [-/US]; 1430 Tulane Avenue, New Orleans, LA 70115 (US). (72) Inventors: COY, David, H. ; 4319 Perrier Street, New Or- leans, LA 70115 (US). MURPHY, William, A. ; 107 N. Magnolia Drive, Covington, LA 70433 (US).		(74) Agent: CLARK, Paul, T.; Fish & Richardson, One Finan- cial Center, Suite 2500, Boston, MA 02111-2658 (US). (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European pa- tent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (Euro- pean patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (Euro- pean patent). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>

(54) Title: OCTAPEPTIDE ANALOGS OF SOMATOSTATIN HAVING THREONINE AT THE SIXTH POSITION



(57) Abstract

A compound of formula (I), wherein each A₁ and A₂, independently, is H C₁₋₁₂ alkyl, C₇₋₁₀ phenylalkyl, R₁CO (where R₁ is C₁₋₂₀ alkyl, C₃₋₂₀ alkenyl, C₃₋₂₀ alkenyl, phenyl, naphthyl, or C₇₋₁₀ phenylalkyl), or R₂OCO (where R is C₁₋₁₀ alkyl or C₇₋₁₀ phenylalkyl), provided that when one of A₁ or A₂ is R₁CO or R₂OCO, the other must be H; each X₁ and X₂, independently, is H, F, Cl, Br, OH, CH₃, or CF₃, provided that at least one of X₁ and X₂ must be H; A₃ is Phe or Tyr; and A₄ is OH, NH₂, or NH-R₃ (wherein R₃ is a saturated aliphatic C₁₋₈ alkyl); or a pharmaceutically acceptable salt thereof; a therapeutic composition comprising such compound; and a method of using such compound.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	SD	Sudan
CF	Central African Republic	KP	Democratic People's Republic of Korea	SE	Sweden
CG	Congo	KR	Republic of Korea	SN	Senegal
CH	Switzerland	LI	Liechtenstein	SU	Soviet Union
CI	Côte d'Ivoire	LK	Sri Lanka	TD	Chad
CM	Cameroon	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark	MG	Madagascar		
ES	Spain				

- 1 -

OCTAPEPTIDE ANALOGS OF SOMATOSTATIN
HAVING THREONINE AT THE SIXTH POSITION

Background of the Invention

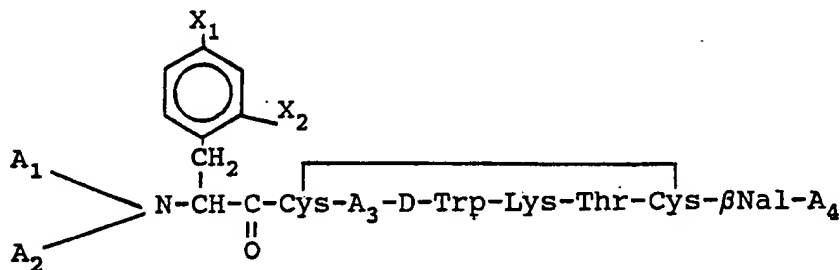
This invention relates to therapeutic peptides.

5 A number of somatostatin analogs exhibiting growth hormone-release-inhibiting activity have been described in the literature, including analogs containing fewer than the naturally-occurring fourteen amino acids. For example, Coy et al., U.S. Patent No. 4,485,101, hereby
10 incorporated by reference, describes dodecapeptides having an amino-terminal acetyl group, a carboxy-terminal amino group, D-Trp at position 6, and p-Cl-Phe at position 4. (The name of each amino acid is herein designated by its standard three-letter abbreviation; the
15 stereoisomeric designation of each amino acid is L unless otherwise specified.)

Summary of the Invention

In general, the invention features a compound of the formula:

20



25

wherein

30

each A_1 and A_2 , independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, R_1CO (where R_1 is C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkenyl, phenyl, naphthyl, or C_{7-10} phenylalkyl), or R_2OCO (where R is C_{1-10} alkyl or C_{7-10} phenylalkyl), provided that when one of A_1 or A_2 is R_1CO or R_2OCO , the other must be H;

- 2 -

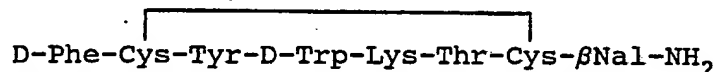
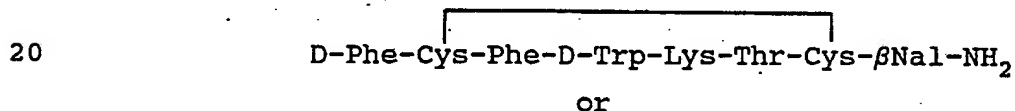
each X_1 and X_2 , independently, is H, F, Cl, Br, OH, CH_3 , or CF_3 , provided that at least one of X_1 and X_2 must be H;

A_3 is Phe or Tyr; and

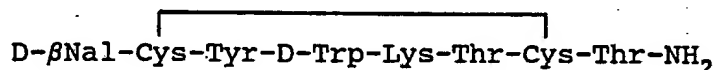
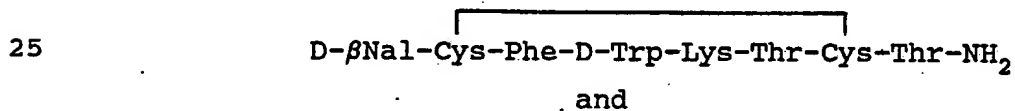
- 5 A_4 is OH, NH_2 , or $NH-R_3$ (wherein R_3 is a saturated aliphatic C_{1-8} alkyl):

or a pharmaceutically acceptable salt thereof. The naturally-occurring amino acids are indicated by their generally-accepted three-letter symbols; unless the D- stereoisomer of an amino acid (other than β Nal) is specified, the L-form is assumed. " β Nal" denotes D- or L- β -naphthylalanine, unless the D- or L- stereoisomer is specified.

15 In preferred embodiments, each A_1 and A_2 , independently, is H or a saturated aliphatic C_{1-3} alkyl; each X_1 and X_2 , independently, is H, F, Cl, or OH, provided that at least one of X_1 and X_2 must be H; and R_3 is saturated aliphatic C_{1-3} alkyl; more preferably, the compound has the formula:



In another aspect, the invention features compounds of the formula:



or a pharmaceutically acceptable salt thereof.

Also featured is a combination of one of the above
30 compounds and a pharmaceutically acceptable carrier

- 3 -

substance in a therapeutic composition capable of inhibiting the release of growth hormone ("GH"), epidermal growth factor, insulin, glucagon, pancreatic exocrine secretions, or substance P, and preferably of
5 GH.

In preferred embodiments, the composition is in the form of a pill, tablet, capsule, or liquid for oral administration; a cream, gel, lotion, spray or ointment for application to the skin of a patient; a liquid
10 capable of being administered nasally as drops or spray; or a liquid capable of intravenous, subcutaneous, parenteral, or intraperitoneal administration. The therapeutic composition can also be in the form of an oil emulsion or dispersion in conjunction with a lipophilic
15 salt such as a pamoic acid, or in the form of a biodegradable sustained-release formulation for subcutaneous or intramuscular administration. For maximum efficacy, zero-order release is desired. Zero-order release can be obtained using an implantable or
20 external pump to administer the therapeutic composition.

The compounds of the invention exhibit a broad range of biological activities related to their antisecretory and antiproliferative properties. The compounds suppress the secretion of several endocrine
25 hormones, including insulin, glucagon, and, in particular, growth hormone (GH). The compounds of the invention also suppress pancreatic and gastric exocrine secretions, and suppress or modulate the release of some neurotransmitters, including substance P and
30 acetylcholine.

The somatostatin analogs can effect tumor cell multiplication by preventing the release of mitotic factors (such as insulin-like growth factor 1 (IGF-1), gastrin-releasing peptides, etc.), and may interfere with
35 the intracellular transduction mechanism, as, for

- 4 -

example, in the case of epidermal growth factor (EGF)-induced cell proliferation.

The aromatic lipophilic N-terminal end can provide long-lasting in vivo activity.

- 5 Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Description of the Preferred Embodiments

Structure

- 10 The compounds of the invention, which are peptide analogs of somatostatin, have the general formula recited in the Summary of the Invention, above.

- The compounds can be provided in the form of pharmaceutically acceptable salts or complexes. As used
15 herein, the term "pharmaceutically acceptable salts or complexes" refers to salts or complexes that retain the desired biological activity of the parent compound and do not impart any undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with
20 inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic
25 acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acids, naphthalenedisulfonic acids, and polygalacturonic acid; (b) base addition salts formed with polyvalent metal cations such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt,
30 nickel, cadmium, and the like, or with an organic cation formed from N,N-dibenzylethylene-diamine or ethylenediamine; or (c) combinations of (a) and (b): e.g., a zinc tannate salt or the like.

- 5 -

Synthesis

The synthesis of one octapeptide follows. Other compounds of the invention can be prepared by making appropriate modifications, within the ability of someone or ordinary skill in this field, or the following synthetic method.

The first step in the preparation of D-Phe-Cys-Phe-D-Trp-Lys-Val-Cys- β Nal-NH₂ was the preparation of the intermediate tert-butyloxycarbonyl-D-Phe-S-methylbenzyl-Cys-Phe-D-Trp-N^ε-benzyloxycarbonyl-Lys-Thr-S-methylbenzyl-Cys- β Nal-NH₂-benzyhydramine resin, as follows.

Methyl-benzyhydramine-polystyrene resin (Advanced Chem-Tech, Inc.) in the chloride ion form was placed in the reaction vessel of a Beckman 990B peptide synthesizer programmed to perform the following reaction cycle: (a) methylene chloride; (b) 33% trifluoroacetic acid in methylene chloride (2 times for 1 and 25 min each); (c) methylene chloride; (d) ethanol; (e) methylene chloride; (f) 10% triethylamine in chloroform.

The neutralized resin was stirred with Boc- β Nal and diisopropylcarbodiimide (1.5 mmole each) in methylene chloride for 1 h and the resulting amino acid resin was then cycled through steps (a) to (f) in the above wash program. The following amino acids (1.5 mmole) were then coupled successively by the same procedure: Boc-S-methylbenzyl-Cys, Boc-Thr, Boc-N^ε-benzyloxycarbonyl-Lysine, Boc-D-trp, Boc-Phe, Boc-S-methylbenzyl-Cys, Boc-D-Phe.

The resin was washed and dried and then mixed with anisole (4 ml) and anhydrous hydrogen fluoride (36 ml) at 0°C and stirred for 45 min. (one can also use thioanisole, trifluoroacetic acid, and trifluoromethane sulfonic acid at a ration of 1:90:9, for 6 h). Excess hydrogen fluoride was evaporated rapidly under a stream

SUBSTITUTE SHEET

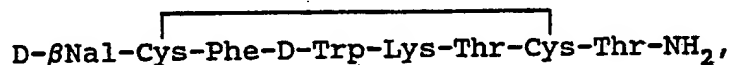
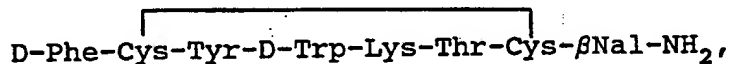
- 6 -

of dry nitrogen and free peptide precipitated and washed with ether. The crude peptide was then dissolved in 800 ml or 90% acetic acid, to which was added I_2 in methanol until a permanent brown color was present. The solution
5 was then stirred for 1 h before removing the solvent in vacuo. The resulting oil was dissolved in a minimum volume of 50% acetic acid and eluted on a column (2.5 X 100 mm) of Sephadex G-25. Fractions containing a major component by UV absorption and thin-layer chromatography
10 were then pooled, evaporated to a small volume, and applied to a column (2.5 X 50 cm) or Vydac octadecylsilane (10-15 μ M).

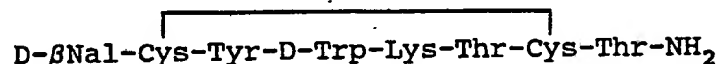
The column was eluted with a linear gradient of 10-50% acetonitrile in 0.1% trifluoroacetic acid in
15 water. Fractions were examined by thin-layer chromatography and analytical high-performance liquid chromatography, pooled to give maximum purity, and, if desired, a different salt prepared, e.g., acetate or phosphate. Repeated lyophilization of the solution from
20 water gave 120 mg of the product as white, fluffy powder.

The product was found to be homogeneous by high-performance liquid chromatography and thin-layer chromatography. Amino acid analysis of an acid hydrolysate confirmed the composition of the octapeptide.

25 Compounds of the invention having the formulas



and



30 were made according to methods analogous to those described above.

- 7 -

Use

When administered to mammals, particularly humans (e.g. orally; topically; intravenously; parenterally in a sustained release, biodegradable form; nasally; or by suppository), the compounds can be effective to inhibit the secretion of various hormones and trophic factors. They may be used to suppress certain endocrine secretions, such as GH, insulin, glucagon and prolactin, the treatment of, for example, acromegaly; endocrine tumors such as carcinoids, vipomas, insulinomas, and glucagonomas; or diabetes and diabetes-related pathologies, including retinopathy, nephropathy, dawn syndrome and type 2 diabetes. The compounds may also be used to suppress exocrine secretions in the pancreas, stomach and intestines, for treatment of, for example, pancreatitis, fistulas, bleeding ulcers, and diarrhea associated with such diseases as AIDS or cholera. Disorders involving autocrine or paracrine secretions of trophic factors such as IGF-1 (as well as some endocrine factors) which may be treated by administration of these compounds include cancers of the breast, prostate, and lung (both small cell and non-small cell epidermoids) as well as hepatomas, neuroblastomas, colon and pancreatic adenocarcinomas (ductal type), chondrosarcomas, and melanomas, and also atherosclerosis associated with vascular grafts and restenosis following angioplasty.

The compounds of the invention also are useful to suppress the mediators of neurogenic inflammation (e.g., substance P or the tachykinins), and thus may be used in the treatment of such pathologies as the rheumatoid arthritis; psoriasis; topical inflammation such as is associated with sunburn, eczema, or other sources of itching; and allergies, including asthma. The compounds also can function as neuromodulators in the central nervous system, with useful applications in the treatment

- 8 -

of Alzheimer's disease and other forms of dementia, pain
(as a spinal analgesic), and headaches. Furthermore, in
disorders involving the splanchnic blood flow, including
cirrhosis, oesophageal varices, and certain cases of
5 mushroom poisoning, the compounds of the invention can
provide cytoprotection.

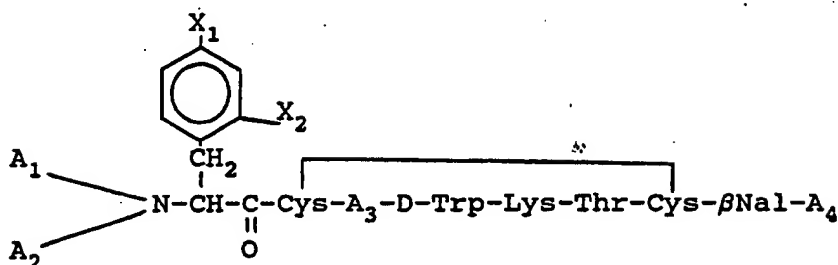
The compounds can be administered to a mammal,
e.g., a human, in a dosage of 0.01 to 50 mg/kg/day,
preferably 0.1 to 5 mg/kg/day.

10 Other embodiments are within the following claims.

- 9 -

Claims

1. A compound of the formula:



wherein

each A_1 and A_2 , independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, R_1CO (where R_1 is C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkenyl, phenyl, naphtyl, or C_{7-10} phenylalkyl), or R_2OCO (where R is C_{1-10} alkyl or C_{7-10} phenylalkyl), provided that when one of A_1 or A_2 is R_1CO or R_2OCO , the other must be H;

each X_1 and X_2 , independently, is H, F, Cl, Br, OH, CH_3 , or CF_3 , provided that at least one of X_1 and X_2 must be H;

A_3 is Phe or Tyr; and

A_4 is OH, NH_2 , or $NH-R_3$ (wherein R_3 is a saturated aliphatic C_{1-8} alkyl);

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein

each A_1 and A_2 , independently, is H of a saturated aliphatic C_{1-3} alkyl;

each X_1 and X_2 , independently, is H, F, Cl, or OH, provided that at least one of X_1 and X_2 must be H; and

R_3 is a saturated aliphatic C_{1-3} alkyl;

or a pharmaceutically acceptable salt thereof.

- 10 -

1 3. The compound of claim 2, wherein said compound
2 has the formula:

3 D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-βNal-NH₂,
4 or a pharmaceutically acceptable salt thereof.

1 4. The compound of claim 2 wherein said compound
2 has the formula:

3 D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-βNal-NH₂,
4 or a pharmaceutically acceptable salt thereof.

1 5. A compound of the formula:

2 D-βNal-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂
3 or

4 D-βNal-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-NH₂,
5 or a pharmaceutically acceptable salt thereof.

1 6. A therapeutic composition capable of
2 inhibiting the release of GH; epidermal growth factor;
3 insulin; glucagon; prolactin; exocrine secretions from
4 the pancreas, stomach or intestines; the tachykinin and
5 substance P, said composition comprising a
6 therapeutically effective amount of the compound of claim
7 1 or claim 5, together with a pharmaceutically acceptable
8 carrier substance.

1 7. The therapeutic composition of claim 6,
2 wherein said composition is capable of inhibiting the
3 release of GH.

1 8. The therapeutic composition of claim 6,
2 wherein said composition is in the form of a liquid,

- 11 -

3 pill, tablet, or capsule for oral administration to a
4 human patient in need of said composition.

1 9. The therapeutic composition of claim 6, said
2 composition being in the form of a cream, gel, lotion,
3 spray, or ointment for application to the skin of a human
4 patient in need of said composition.

1 10. The therapeutic composition of claim 6, said
2 composition being in the form of a liquid capable of
3 being administered nasally as drops or spray to a human
4 patient in need of said composition.

1 11. The therapeutic composition of claim 6, said
2 composition being in the form of a liquid for
3 intravenous, subcutaneous, parenteral, or intraperitoneal
4 administration to a human patient in need of said
5 composition.

1 12. The therapeutic composition of claim 6, said
2 composition being in the form of a biodegradable
3 sustained-release composition for intramuscular
4 administration to a human patient in need of said
5 composition.

1 13. The therapeutic composition of claim 6,
2 wherein said composition includes a lipophilic salt and
3 is suitable for administration in the form of an oil
4 emulsion or dispersion to a human patient in need of said
5 composition.

1 14. A method of treating a mammal in need of
2 reduction of GH; epidermal growth factor; insulin;
3 glucagon; prolactin; exocrine secretions from the
4 pancreas, stomach or intestines; the tachykinin and

- 12 -

5 substance P, said method comprising administering to said
6 mammal a therapeutically effective amount of the compound
7 of claim 1 or claim 5.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/07074

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5):C07K 7/26; A61K 37/02 U.S. CL.: 530/311, 328, 317; 514/16																				
II. FIELDS SEARCHED <div style="display: flex; justify-content: space-between; border-bottom: 1px solid black; margin-bottom: 5px;"> Classification System Minimum Documentation Searched ⁷ </div> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 20%; border: 1px solid black; padding: 5px; vertical-align: top;">U.S.</td> <td style="border: 1px solid black; padding: 5px; vertical-align: top;">530/311, 328, 317; 514/16</td> </tr> </table> <div style="border: 1px solid black; padding: 5px; margin-top: 5px;"> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸ </div>			U.S.	530/311, 328, 317; 514/16																
U.S.	530/311, 328, 317; 514/16																			
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <thead> <tr> <th style="width: 10%; padding: 5px;">Category ⁹</th> <th style="width: 70%; padding: 5px;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; padding: 5px;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">US. A. 4,328,135 (SARANTAKIS), 04 May 1982, see the entire document.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1 & 6-14</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">US, A. 4,435,385 (BAUER et al), 06 March 1984, see the entire document.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1 & 6-14</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">US, A. 4,485,101 (COY et al), 27 November 1984, see the entire document.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1 & 6-14</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">US, A. 4,853,371 (COY et al), 01 August 1989, see col. 1, lines 25-49; col. 2, lines 5-37.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1 & 6-14</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">Proceedings 9th Annual Peptide Symposium Abstract, issued July 1985, Cai et al., "Synthesis and evaluation of activities of octapeptide analogs of Somatostatin", pp. 627-630, particularly page 628.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1, 3 & 6-14</td> </tr> </tbody> </table> <div style="margin-top: 10px;"> <div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div> </div>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	US. A. 4,328,135 (SARANTAKIS), 04 May 1982, see the entire document.	1 & 6-14	A	US, A. 4,435,385 (BAUER et al), 06 March 1984, see the entire document.	1 & 6-14	A	US, A. 4,485,101 (COY et al), 27 November 1984, see the entire document.	1 & 6-14	Y	US, A. 4,853,371 (COY et al), 01 August 1989, see col. 1, lines 25-49; col. 2, lines 5-37.	1 & 6-14	Y	Proceedings 9th Annual Peptide Symposium Abstract, issued July 1985, Cai et al., "Synthesis and evaluation of activities of octapeptide analogs of Somatostatin", pp. 627-630, particularly page 628.	1, 3 & 6-14
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³																		
A	US. A. 4,328,135 (SARANTAKIS), 04 May 1982, see the entire document.	1 & 6-14																		
A	US, A. 4,435,385 (BAUER et al), 06 March 1984, see the entire document.	1 & 6-14																		
A	US, A. 4,485,101 (COY et al), 27 November 1984, see the entire document.	1 & 6-14																		
Y	US, A. 4,853,371 (COY et al), 01 August 1989, see col. 1, lines 25-49; col. 2, lines 5-37.	1 & 6-14																		
Y	Proceedings 9th Annual Peptide Symposium Abstract, issued July 1985, Cai et al., "Synthesis and evaluation of activities of octapeptide analogs of Somatostatin", pp. 627-630, particularly page 628.	1, 3 & 6-14																		
IV. CERTIFICATION Date of the Actual Completion of the International Search <div style="text-align: center; margin-top: 10px;">14 March 1991</div>		Date of Mailing of this International Search Report <div style="text-align: center; margin-top: 10px;"> <div style="border: 1px solid black; padding: 2px; display: inline-block;">29 APR 1991</div> </div>																		
International Searching Authority <div style="text-align: center; margin-top: 10px;">ISA/US</div>		Signature of Authorized Officer <div style="text-align: center; margin-top: 10px;"> <div style="display: flex; align-items: center; justify-content: center;"> T.D. Wessendorf ebw </div> </div>																		

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____, because they relate to subject matter ¹² not required to be searched by this Authority, namely:

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹³, specifically:

3. ☐ Claim numbers _____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

See attachment

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
1 and 6-14 (First listed specie) Telephone Practice.
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Attachment to PCT/ISA/210

This application is directed to a generic inventions containing multiple species.

Applicants are required to elect disclosed specie from the claimed genus. For example, a single definition for each of the given variables like A_1 definition H; $A_2=H$, $A_3= PHe$, $A_4=OH;X, =H$; $X_2=F$; etc. or species from claims 3-5.

Each of the species comprised in the genus are distinct since they are physically or structurally dissimilar. One specie in the claimed genus containing specific definitions for each variables would not suggest the other species containing different definitions for the same given variable(s).

In conformance with PCT Rule 13.1, the composition comprising the peptide (specie) and method of using said peptide i.e. claims 6 -14 would be examined with the elected (peptide) specie.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. Wessendorf whose telephone number is (703) 308-3697.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 309-0196.

THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)